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14. ABSTRACT This proposal is driven by hypothesis that certain biological factors associated with metabolic syndrome may play a role in racial differences in prostate cancer (PCa) aggressiveness and prognosis. This is the first study to include large numbers of African American men in an evaluation of metabolic syndrome and the first to study the association between metabolic syndrome and PCa recurrence by race. Our hypothesis is being tested in 2 Aims: 1) To quantitatively assess levels of multimeric adiponectin complexes and selected biochemical markers related to inflammation, insulin resistance and oxidative stress in serum of newly diagnosed PCa patients with non-aggressive and aggressive disease, and examine racial differences in statistical correlations between these biomarkers and adiponectin in PCa patients with aggressive disease; and 2) determine if there are differences in single nucleotide polymorphisms (SNPs) in selected candidate genes implicated in metabolic syndrome, obesity, chronic inflammation inflammation, and oxidative stress in PCa patients with aggressive and non-aggressive disease, and determine how these differences predict the risk of aggressive PCa and disease recurrence by race. We predict that this work should identify novel biomarkers for detection and prognosis of aggressive PCa and provide basis for future studies of mechanisms that drive racial disparities in PCa aggressiveness and outcome.					
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INTRODUCTION:

Emerging data suggest that obesity and metabolic syndrome contribute to an increased risk of prostate cancer [1-8]. African American men are predisposed to specific features of metabolic syndrome, such as hypertension and abdominal obesity, which are also risk factors for PCa in this racial group [9, 10]. The proposed studies will test the hypothesis that specific biochemical and genetic factors related to inflammation, insulin resistance and oxidative stress, contribute to racial/ethnic disparity in aggressiveness and recurrence of PCa. Predisposition of African Americans to hypertension and vascular dysfunction has been linked to suppressed levels of the hormone adiponectin and increased levels of markers of systemic inflammation [11, 12]. Recent data also suggest that distribution of different multimeric forms of adiponectin (as opposed to total protein levels) may be reflective of insulin resistance and oxidative stress [13, 14]. This suggests that certain biological factors associated with metabolic syndrome may play a role in racial differences in PCa aggressiveness and prognosis.

The present study is based on the hypothesis that specific biochemical and genetic factors contribute to racial/ethnic disparity in aggressiveness and recurrence of PCa. Our specific aims are to: 1) quantitatively assess levels and distribution of multimeric adiponectin complexes and selected biochemical markers related to inflammation, insulin resistance and oxidative stress in serum of newly diagnosed PCa patients with non-aggressive and aggressive disease, and examine racial differences in statistical correlations between these biomarkers and adiponectin in PCa patients with aggressive disease; and 2) determine if there are differences in single nucleotide polymorphisms (SNPs) in selected candidate genes implicated in metabolic syndrome, obesity, chronic inflammation, and oxidative stress in prostate cancer patients with aggressive and non-aggressive disease, and determine how these differences predict the risk of aggressive prostate cancer and disease recurrence by race. To achieve these aims we are: 1) utilizing Adiponectin (Multimeric) Enzyme Immunoassays for quantitative assessment of levels and distribution of multimeric forms of adiponectin in serum; 2) assessing levels of 15 biomarkers implicated in inflammation, insulin resistance and oxidative stress using Custom Quantitative Antibody Arrays; 3) examining the statistical relationships between adiponectin and these biomarkers in predicting racial differences in prostate cancer aggressiveness and prognosis using scatterplots as a statistical graphic, and Pearson product moment correlation coefficients as measures of the strength of linear association; 4) performing SNP analyses and assessments of allele frequency differences in 34 genes involved in various pathways including obesity, inflammation, insulin resistance and oxidative stress using Illumina GoldenGate assays; and 5) employing a logistic regression model to estimate the risk of aggressive prostate cancer associated with each genotype by race, and a Cox Proportional hazards modeling approach to estimate the risk of recurrence associated with each genotype by race.

We predict that these studies will confirm our hypothesis that metabolic syndrome-induced inflammation, insulin resistance and oxidative stress differentially influence disease progression in African American and European American men. This work should identify novel biomarkers for detection and prognosis of aggressive prostate cancer. Results of this study will provide the basis for future validation of these biomarkers as biological targets for improved therapy and/or prevention of aggressive disease, and studies of novel signaling pathways and the molecular mechanisms that contribute to aggressiveness of prostate cancer.

BODY:

In year two of this study, we continued to recruit patients and collect samples for the serum and SNP analyses. These samples are being collected under the parent DoD Health Disparity grant (PC081618), that begun in July 2009, and is led by Dr. I. Powell. The accrual goal for this study is 500

or more patients. For Task 1, only cases diagnosed on or after September 1st, 2009 (newly diagnosed patients) are being included in the analysis. For the genomic DNA analyses described in Task 2, all patients recruited into PC081618 (i.e., prostate cancer cases diagnosed on or after January 1st, 2004) are eligible for inclusion. Since the goal of 500 patients was recently reached, our focus now is on the analysis of levels biochemical markers in serum and their correlation with clinical features. The characteristics of our study population based on 476 patients analyzed to date are shown in Table 1. The average age at diagnosis is 61 years and 62% of patients are African American.

Table 1. Prostate cancer patients enrolled in the metabolic syndrome investigation

Feature	All Patients N=476	African American N=316	Caucasian N=160
Advanced stage Gleason \geq 4+3	36.7% 35.7%	33.0% 32.4%	42.3% 41.7%
Hypertension	70.9%	75.5%	60.3%
Diabetes	24.0%	26.5%	18.7%
High Cholesterol	58.4%	54.4%	65.4%
Obesity	40.2%	38.1%	44.0%
Metabolic Syndrome (3+features)	30.7%	33.5%	26.1%

TASK 1: We will quantitatively assess levels and distribution of multimeric adiponectin complexes and selected biochemical markers related to inflammation, insulin resistance and oxidative stress in serum of newly diagnosed PCa patients with non-aggressive and aggressive disease, and examine statistical correlations between these biomarkers in predicting racial differences in PCa aggressiveness and prognosis.

Sub-Aim 1A: To explore biochemical markers that predict PCa aggressiveness, we will quantitatively assess serum levels of 15 cytokines related to inflammation, insulin resistance and oxidative stress and correlate them with levels and distribution of multimeric complexes of adiponectin in non-aggressive (n=45) and aggressive (n=45) patients).

Sub-Aim 1B: To explore racial differences in aggressive PCa we will determine cytokine levels and their correlations with adiponectin complexes in AA (n=45) vs. EA (n =45) men with aggressive disease. We will further stratify the results based on prevalence of metabolic syndrome to assess the differential influence of metabolic syndrome-induced inflammation, insulin resistance and oxidative stress on disease progression between AA and EA

Serum cytokine levels: In last year's report, we showed preliminary results on inflammatory markers

in serum of 23 newly diagnosed PCa patients. These were mainly feasibility studies demonstrating our ability to detect the inflammatory factors in serum samples using quantitative, fluorescent antibody arrays. We have since repeated these studies in 41 newly diagnosed PCa patients and analyzed the results based on race, metabolic syndrome, and aggressive disease status (Table 2). Levels of MCP-1 (Macrophage Chemoattractant Protein -1) and MCP-3 (Macrophage Chemoattractant Protein -3) and Oncostatin M (cytokine in the IL-6 family) differed most according to race. GRO; leptin and PDGFBB showed trends of differential distribution based on metabolic syndrome status but the differences were not significant.

Table 2. Most differentially distributed cytokines in serum of newly diagnosed PCa patients

STATUS	CYTOKINE	Significant t-test p-value	Significant mwu p-value
AGGRESSIVENESS	Leptin	0.035	0.057
	MCP3	0.095	
	MCP-1	0.045	0.069
	MIP-1 delta	0.089	
	Oncostatin M	0.042	0.065
METABOLIC SYNDROME	GRO	0.075	
	Leptin	0.075	
	PDGF BB	0.1	
RACE	MCP3	0.02	0.018
	MCP-1	0.025	0.038
	Oncostatin M	0.021	0.048
	IL-1		0.069

We performed additional analyses for MCP-1 and MCP-3 according to patient's metabolic syndrome status (3 or more features), obesity, hypertension and aggressive disease. Levels MCP-1 exhibit higher trends in European American patients with metabolic syndrome, as well as aggressive disease (Figure 1).

MACROPHAGE CHEMOATTRACTANT PROTEIN 1 (MCP-1; CCL2)

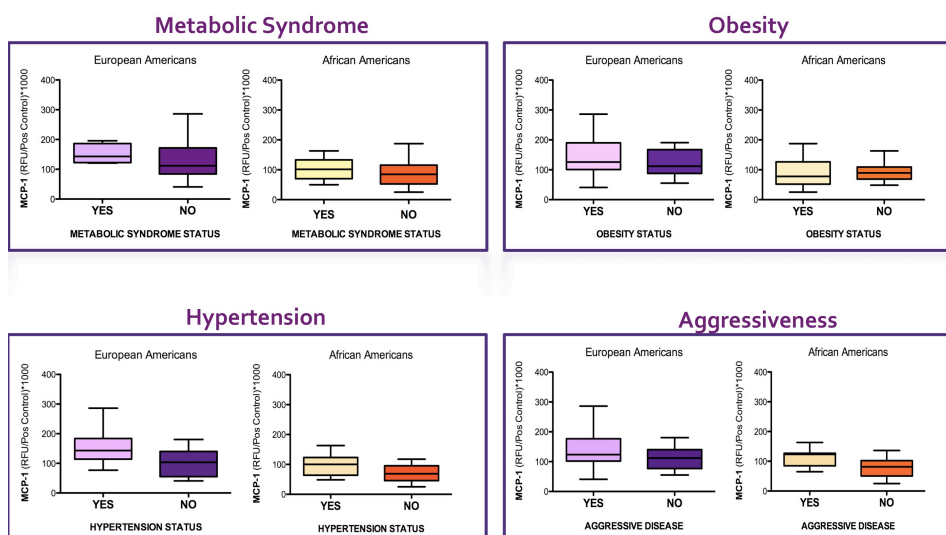


Figure 1. Levels of MCP1 in newly diagnosed PCa patients. Results of fluorescent cytokine arrays analyzed based on race, metabolic syndrome status and aggressive disease and shown as relative fluorescent units (RFU) normalized to positive controls.

With respect to MCP3 (an inflammatory cytokine related to MCP1), overall higher levels were detected in African American PCa patients, with some differences depending on the metabolic syndrome status and disease aggressiveness. For European American patients, MCP3 levels remained low irrespective of metabolic syndrome, obesity, hypertension or PCa aggressiveness status. These data encourage additional investigations into these two pro-inflammatory cytokines. Custom fully quantitative cytokine arrays as well as ELISA assays are currently being used to validate these findings and further explore potential biomarker suitability of MCP1 and MCP3.

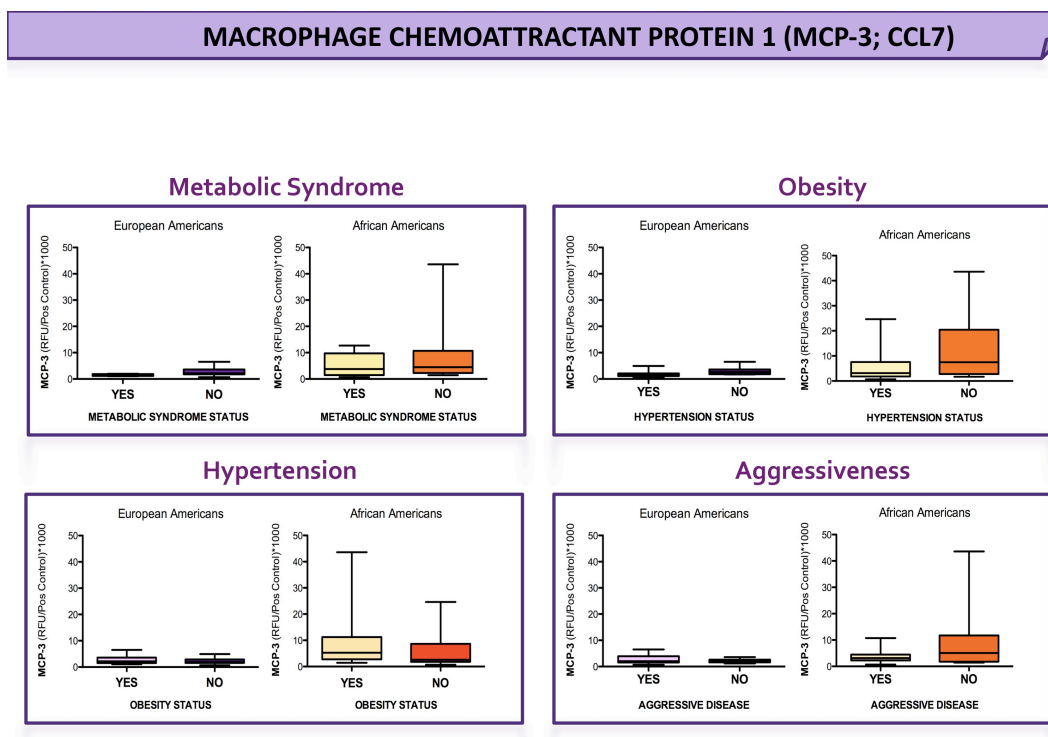


Figure 2. Levels of MCP3 in newly diagnosed PCa patients. Results fluorescent cytokine arrays analyzed based on race, metabolic syndrome status and aggressive disease and shown as relative fluorescent units (RFU) normalized to positive controls.

Serum adiponectin levels: In last year's report we included preliminary results on adiponectin levels in serum of 16 PCa patients. The goal of these studies is to investigate the distribution of total and high molecular adiponectin (HMW) levels in serum of PCa patients as predictors of metabolic syndrome and links to racial disparities in aggressive disease. We have since expanded this analysis to 41 newly diagnosed patients and analyzed the results based on metabolic syndrome features and hypertension status. Lower levels of total and especially HMW adiponectin are observed in patients with metabolic syndrome and hypertension, results in agreement with literature reports linking low adiponectin levels with insulin resistance and cardiovascular risks. We are still in process of performing these analyses in a larger group of patients and we are investigating these results based on race and aggressive disease status. Correlative analyses of adiponectin levels and select inflammatory markers in serum are also in progress.

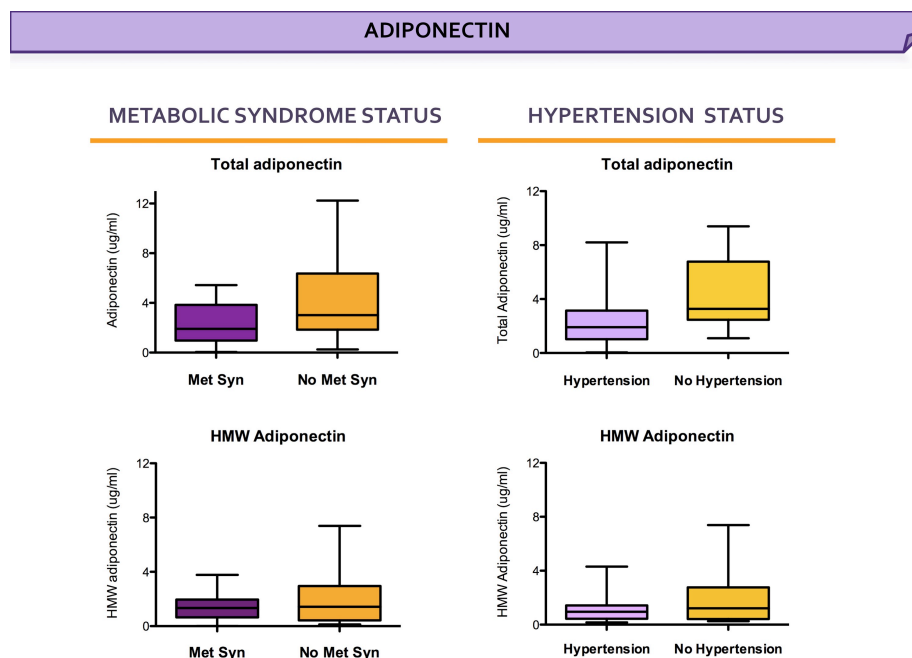


Figure 3. Levels of total and HMW adiponectin in serum of newly diagnosed PCa patients. ELISA results analyzed based on metabolic syndrome and hypertension status and expressed in ug/ml.

TASK 2: We will determine if there are differences in the single nucleotide polymorphisms (SNPs) in selected candidate genes implicated in metabolic syndrome, obesity, chronic inflammation, and oxidative stress in PCa patients with aggressive and non-aggressive disease, and determine how these differences predict the risk of aggressive PCa and disease recurrence by race.

Sub-Aim1: To explore genetic markers that may predict PCa aggressiveness, we will examine differences in allele frequency in 34 genes involved in various pathways including obesity, inflammation, insulin resistance and oxidative stress between PCa cases diagnosed with aggressive disease and cases considered non-aggressive.

Sub-Aim 2: To explore genetic markers that may predict PCa recurrence, we will examine differences in allele frequency in 34 genes involved in various pathways including obesity, inflammation, insulin resistance and oxidative stress between prostate cancer cases with evidence of disease recurrence and non-recurring cases.

We have proposed to investigate differences in allele frequency in genes involved in various pathways including obesity, inflammation, insulin resistance and oxidative stress and correlate them with PCa aggressiveness and recurrence. We proposed to perform this analysis on all 500 DNA samples collected for this study. As the recruitment has now been completed, we are currently finalizing the list of tagSNPs within the genes from the pathways of interest using Tagger <<http://www.broadinstitute.org/mpg/tagger/>>. Genotype of tagSNPs will be determined using a custom

panel run on the Illumina GoldenGate® genotyping platform. Haplotypes will be constructed using Haploview. We will examine the association between SNPs in selected candidate genes and aggressive prostate cancer as well as disease recurrence. These analyses are expected to be completed by the end of 2012. We anticipate that differences in allele frequency exist between aggressive prostate cancer cases and non-aggressive cases in genes involved in insulin resistance, inflammatory and oxidative stress pathways. We predict that these pathways influence prostate cancer progression and therefore would predict aggressive disease and prognosis.

KEY RESEARCH ACCOMPLISHMENTS:

- We have successfully completed the recruitment of PCa patients to this study
- The percentage of participation for African American patients is high (62%), which gives us a unique opportunity to study the mechanisms behind PCa aggressiveness and potential for recurrence in this population
- Our preliminary results suggest there may be some racial differences in select serum markers with disease aggressiveness and specific metabolic syndrome features
- Our data suggest that levels of total and HMW adiponectin are lower in patients with hypertension and metabolic syndrome.
- Studies of serum markers in complete set of newly diagnosed patients are currently ongoing; completion of analyses expected in early 2013
- We are preparing for tagSNP analyses using DNA samples from all patients recruited to this study. List of tagSNP within the genes from the pathways of interest is being finalized and completion of analysis is expected by end of 2012.

REPORTABLE OUTCOMES:

1. Invited Lectures/Presentations at National/International Meetings

- A. "Protease-adipokine signaling in bone metastasis." **Gordon Research Conference on Proteolytic Enzymes and Their Inhibitors**. Lucca, Italy, May 2-7, 2010.
- B. "Delayed Progression of Prostate Bone Tumors in Cathepsin K-deficient Mice: Novel Proteolytic Pathways and Adipocyte Involvement in the Bone Microenvironment." **Department of Defense Prostate Cancer IMPaCT Conference**, Orlando Florida, March 9-12, 2011

2. Invited/Refereed Presentations at Local/Regional Meetings

- A. "Exploring the Links between Obesity, Inflammation, Metabolic Syndrome and Prostate Cancer". **Presentation for Carla G. Hawley-Bowland, Medical Corps General**, during her visit related to Army Physician in Training Program, October 5, 2010.
- B. "Proteolytic and Inflammatory Pathways in Bone Metastasis: Lessons From Cathepsin K Knockout Mice." **Joint Retreat of Proteases and Cancer and Breast Cancer Programs at Karmanos Cancer Institute**; Detroit, MI, December 14, 2010.
- C. "Biochemical markers of inflammation and racial disparities in prostate cancer" **Karmanos Cancer Institute Ground Rounds**, November 3, 2011.
- D. "Adipocytes, bone marrow inflammation, and progression of prostate tumors in bone: Does cathepsin K play a role? **University of Toledo, Department of Pharmacology seminar series**, November 9, 2011
- E. "Exploring inflammatory pathways linking metabolic syndrome with racial disparities in prostate cancer", **Karmanos Cancer Institute Research Retreat**, May 9, 2012
- F. "Adipocytes, bone marrow inflammation, and progression of prostate tumors in bone"; University of Michigan, July 9, 2012

3. Abstracts:

- A. Sreeker Reddy, Mackenzie Herroon, and Izabela Podgorski. Analyzing the Effects of Adipocyte Conditioned Media on Bone Metastatic Cell Lines. **Summer Undergraduate Student Poster Day**, Wayne State University, August 10, 2010.
- B. Izabela Podgorski, Mackenzie Heroon, Deborah Rudy, Anju Mukundan, and Craig Giroux. Delayed Progression of Prostate Bone Tumors in Cathepsin K-deficient Mice: Distinct Effects on Tumor- and Host-Initiated proteolytic Pathways. **Metastasis Research Society and AACR Joint Conference on Metastasis and Tumor Microenvironment**. Philadelphia, PA, September 12-15, 2010.

- C. Aimalie Hardaway, Katelyn Powell, Mackenzie Herroon, and **Izabela Podgorski**. "Role of adipocyte-derived factors in prostate cancer bone metastasis." **Wayne State Graduate Exhibition**, March 2nd, 2011, **2nd place winner**.
- D. **Izabela Podgorski**, Mackenzie Herroon, Craig Giroux, James Grannneman, Deborah Rudy, Anju Mukundan. Delayed Progression of Prostate Bone Tumors in Cathepsin K-deficient Mice: Novel Proteolytic Pathways and Adipocyte Involvement in the Bone Microenvironment. **Department of Defense Prostate Cancer IMPaCT Conference**, Orlando Florida, March 9-12, 2011; **Abstract selected for podium presentation**.
- E. Jennifer Beebe-Dimmer, Cathryn Bock, **Izabela Podgorski**, Susan Bolton, Sarah Lewis, and Isaac Powell. The Influence of Metabolic Syndrome on Prostate Cancer Progression and Risk of recurrence in African American and European American Men" **Department of Defense Prostate Cancer . IMPaCT Conference**, Orlando Florida, March 9-12, 2011.
- F. Aimalie L. Hardaway*, Katelyn A. Powell*, Mackenzie K. Herroon, Erandi N. Rajagurubandara, and **Izabela Podgorski** . "Inflammation and Oxidative Stress in Prostate Cancer Bone Metastasis: Contribution of Bone Marrow Adipocytes"; **KCI Proteases and Cancer Program Annual Retreat**, December, 2011
- G. Aimalie L. Hardaway*, Mackenzie K. Herroon, Erandi N. Rajagurubandara, Gorica Ristic*, and **Izabela Podgorski**. "Inflammation and Obesity in Prostate Cancer Bone Metastasis: Role of Bone Marrow Macrophages". **3rd Annual Graduate Exhibition**, March 6, 2012
- H. Aimalie Hardaway*, Mackenzie, K Herroon, Erandi Rajagurubandara, Audrey Turchick*, and **Izabela Podgorski**. The Role of Bone Marrow Adipocyte-Induced HO-1 Expression Prostate Tumor Survival in Bone. **AACR Annual Meeting**, Chicago, IL, March 31- April 4, 2012.

4. Recent Publications

1. Trivedi, E.R., Harney, A.S, Olive, M.B, **Podgorski, I.**, Moin, K., Sloane, B.F., Barrett, A., Meade, T.J., Hoffman, B.M. Chiral Porphyrazines as Near-Infrared Optical Contrast Agents: Tumor Specific Accumulation In Vivo, *PNAS*, 107(4):1284-8, **2010** [PMID: 20080563](#)
2. **Podgorski, I.**, Inhibiting Cysteine Cathepsins in the Bone, New Functions and Off-Target Effects. *Clinical Reviews in Bone and Mineral Metabolism*; 9(2):81-82, **2011** [CRBMM](#)
3. Respondek, T., Garner, R., Herroon, M.K., **Podgorski, I.**, Turro, C., and Kodanko, J. Light Activation of a Cysteine Protease Inhibitor: Caging of a Peptidomimetic Nitrile by Ru(bpy)²⁺. *Journal of American Chemical Society* 133(43):17164-12167 [PMID: 21973207](#).
4. Herroon, M.K., Rajagurubandara, E., Rudy, D.L., Chalasani, A., Hardaway, A., and **Podgorski, I.** Macrophage Cathepsin K Promotes Prostate Tumor Progression in Bone. *Oncogene* **2012** (epub ahead of print).

3. Other Active grants:

1. “The Influence of Metabolic Syndrome on Prostate Cancer progression and Risk of Recurrence in African American and Caucasian Men.” DoD Health Disparity Award; 4/1/09-8/31/12; **Role: Consultant**
2. “Combination of Imaging and Genomic Approaches to Identify Bone and Tumor Responses to RTK-Targeted Therapy for Metastatic Prostate Cancer.” NOMIC Award /Karmanos Cancer Institute; 6/16/11-6/15/14; **Role: PI**
3. Herrick Foundation/KCI – Prostate Cancer Research Initiatives “Racial Disparities, Metabolic Syndrome, Inflammation and Prostate Cancer Outcomes.” 10/01/09 – 9/30/14. **Role: Co-PI**

CONCLUSIONS:

The overall goal of this study is to examine the association between metabolic syndrome and related conditions such as inflammation, insulin resistance and oxidative stress, and aggressive prostate cancer (PCa). The study is based on hypothesis that specific biochemical and genetic factors contribute to racial/ethnic disparity in aggressiveness and recurrence of PCa. We are utilizing an invaluable resource of blood samples collected from a large group of African American and European American prostate cancer patients; we are using this resource to explore biochemical and genetic markers of aggressive disease; no study to date has systematically addressed the issue of metabolic syndrome in predicting risk of developing aggressive versus non-aggressive disease and prostate cancer recurrence in any racial group.

We have successfully completed the patient recruitment to this study. Our patient population with 62% African American participation gives us a unique opportunity to study the racial disparities behind PCa aggressiveness and potential for recurrence. We have begun exploration of biochemical markers in serum and our preliminary results indicate potential racial differences in metabolic syndrome features and PCa aggressiveness. We are now expanding these studies to all newly diagnosed patients in our recruited patient population and we are correlating the results with clinical data (metabolic syndrome status, race, disease aggressiveness). Analyses of DNA samples from all recruited PCa patients are also underway. The list tagSNPs within the genes from our inflammation-, obesity- and oxidative stress-related pathways is currently being finalized, and analyses are expected to be completed by the end of 2012.

We expect our studies are likely to identify novel biochemical and genetic markers for detection and prognosis of aggressive prostate cancer, and provide the basis for future validation of these biomarkers as biological targets for improved therapy and/or prevention of aggressive disease.

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